REMARKS

In the claims:

The Examiner has objected to claims 16, 31 and 35 because of a typographical error appearing in the term "Islets of Langerhans". This expression has now been corrected. Moreover, claim 36 presently on file has been deleted.

Response to the rejection under 35 USC § 112

The Applicants have noted the Examiner's rejection of claim 36 under 35 USC § 112, first paragraph. Claim 36 has been deleted hence its rejection has been rendered moot.

Response to the rejection under 35 USC § 102

The Applicants have noted the Examiner's rejection of claims 17, 18, 20 to 22 and 27 to 31 under 35 USC § 102 as being anticipated by Chang et al.

The Applicants contest this rejection and wish to remind the Examiner that one inventive feature of the microcapsule of the invention is the presence of covalent links between the molecules of the semi-permeable membrane (poly (L-Lysine)) and the beaded material and the molecules of the semi-permeable membrane and the molecules of the biocompatible layer such as alginate. Therefore the covalent links are between two molecules of different types, which advantageously provide the microcapsule of the invention with increased resistance to physical and chemical stress.

On the other hand Chang et al., while they disclose a semi-permeable microcapsule comprising a bead (alginate-poly L-lysine gel core or droplets) suited to enclose a material, a semi-permeable layer covering the bead, and the said semi-permeable layer being made of a polycation cross-linking derivative such as α-phenylcinnamylideneacetylated poly L-lysine used as a photosensitive poly (L-lysine) product, they do not teach nor suggest to provide a microcapsule comprising covalent links between the semi-permeable layer and the bead and between the semi-permeable layer and the biocompatible layer. Also, contrary to what is stated by the Examiner on

page 7 of the Office Action, Chang et al. do not teach the presence of covalent links between the biocompatible layer and the polycation cross-linking derivative of said semi-permeable layer. Indeed, Chang et al. mention on page 124 (right column) that:

> *"the strengthening process is based on the ionic interaction between photosensitive PLL and alginate followed by the dimerization of photosensitive poly(L-Lysine)."* (underlining is ours)

Hence, Chang et al. clearly state that the links between the different layers is ionic in nature, which is contrary to the teaching of the present invention.

It is also clear from Chang et al. that the photoactivated reaction does not induce a reaction between two different polymers. It is a photodimerization reaction between two molecules of the same polymer. This polymer being α-phenylcinnamylideneacetylatedpoly-L-lysine.

Moreover, the Applicants wish to bring to the attention of the Examiner that the presence of the covalent bonds between the biocompatible layer and the semi-permeable layer and between the semi-permeable layer and the bead result in an increased microcapsule strength as such is demonstrated in Example 4 of the specification of the present invention. In this example, it is shown that the microcapsules when submitted to continuous shaking on a rotary vertical agitator at 35 rpm for 72 hrs in the presence of glass beads, the percentage of broken capsules was about 22 fold lower with the capsules of the invention than with controls. In other words, one skilled in the art would understand that the capsules of the present invention are 22 fold more resistant than the controls, whereas Chang's microcapsules were 2 fold more resistant than controls (i.e. 50% of broken capsules). As the Examiner may appreciate, the "microcapsule mechanical resistance" test used by the Applicants is more severe in terms of mechanical force applied on the microcapsule than the one used by Chang et al. Indeed, the Applicants have used glass beads, which add shearing force on the microcapsules of the invention. This additional shearing force was not present in the test disclosed in the document by Chang et al. Moreover, when submitted to a strong alkaline medium (pH 13) as shown in example 3 of the instant specification, the microcapsules of the present invention remained intact up to

2 years whereas standard microcapsules completely dissolved within 45 sec in the same solution.

Hence the microcapsule of the invention presents higher resistance to shear stress than the capsules of the prior art cited such as those of Chang et al.

It is thus clear from the above arguments that the document by Chang et al. does disclose a microcapsule readily distinguishable from the one of the present invention and claimed in claims 17 and 18.

Hence claims 17 and 18 are new and inventive in view of this prior art.

Moreover, the Applicants submit that claims 20 to 22 and 27 to 31, which are dependant on claim 17, are also new and inventive in view of the prior art.

The Examiner is thus respectfully requested to reconsider this rejection.

Response to the rejections under 35 USC § 103

First, the Applicants would like to remind the Examiner's that claim 36 has been deleted, hence its rejection for lack of inventive activity under 35 USC § 103 has been rendered moot and will not be discussed.

The Applicants have noted the Examiner's rejection for lack of inventive activity under 35 USC § 103 of claims 32 to 35 set forth on page 10 to 13 of the Office Action and of claims 1, 2, 4 to 9 and 14 to 16 set forth on page 24 of the Office Action in view of Chang et al. as applied to claims 17, 18, 20 to 22 and 27 to 38 and in view of Hubbell et al.

The Applicants have also noted the Examiner's rejection of claims 19 and 23 to 26 for lack of inventive activity in view of Chang et al. and Pierce Biotechnology Inc. under 35 USC § 103 as set forth on page 16 of the Office Action.

Finally, the Applicants have further noted the Examiner's rejection of claims 3 and 10

to 13 for lack of inventive activity in view of Chang et al., Hubbell et al and Pierce Biotechnology Inc. under 35 USC § 103 as set forth on page 25 of the Office Action.

The Applicants respectfully disagree with the Examiner for the following reasons. As mentioned above, the present invention is directed to a method of microencapsulating beaded material in which the beaded material is covered with a semi-permeable layer made of a polycation cross-linking derivative preferably poly L-lysine and ANB-NOS, the semi-permeable layer is covered with a biocompatible layer preferably of alginate. The semi-permeable layer is covalently linked to the beaded material and to the biocompatible layer. The present invention is also directed to a microcapsule made by the method of the invention and to a pharmaceutical composition containing a plurality of microcapsules of the invention.

First, the Applicants would like to draw the Examiner's attention to the fact that all claims directly or indirectly dependant on claim 17 should be considered inventive in view of Chang et al., since claim 17 is new and inventive in view of Chang et al.

Moreover, the Examiner is reminded that Chang et al. teach a microcapsule exhibiting ionic bonds between photosensitive poly L-lysine and alginate. As the Examiner admits on page 20, lines 17 to 19 of the Office Action, *the method for microencapsulating a beaded material comprising a step of "providing a material enclosed within a bead" is not explicitly disclosed by Chang et al.*

Hubbell et al. teach a composition comprising a microcapsule in a pharmaceutically acceptable carrier such as HEPES buffered saline, enclosing biological material.

The document by Pierce Biotechnology, Inc. merely discloses that this commercial company sells photoactivable cross linkers such as ANB-NOS. However and as admitted by the Examiner, on page 19, line 2, such cross linkers are known in extensive cross-linkers of proteins. These cross-linkers are used for studies in proteins biochemistry more specifically for intracellular protein studies. Although Pierce Biotechnology, Inc. proposes and sells the product and describes its characteristics, it does not propose an application for its use in the art of the present invention nor does

it mention the conditions of use in the field of microencapsulation. Chemical cross linking agents of Pierce Biotechnology Inc. are usually used to determine near neighbor relationships, analyze three-dimensional structures of proteins and complexes, prepare antibody-enzyme conjugates, immobilize molecules and conjugate chaperone to carrier proteins. Contrary to the document by Chang et al., the document by Pierce Biotechnology Inc. cannot be considered as being a relevant prior art in the field of encapsulation.

The Examiner is also reminded that in *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1385 (Fed. Cir. 20010), it is said that:

> *"In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation, or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention."*

In the present case, the Applicants are of the opinion that there is no suggestion, motivation or teaching in the prior art that would have led a person of ordinary skill to select Hubbell et al. and/or the document by Pierce Biotechnology Inc. and combining them with Chang et al.

It is thus clear from the above arguments that by combining the teaching of Chang et al. to any of the two other cited prior art documents, a person skilled in the art would be led to produce a microcapsule comprising ionic bonds between photosensitive poly-lysine and alginate. Therefore, such a person would never have arrived to the microcapsule or the pharmaceutical composition of the invention nor would such a person have arrived to the method for the microencapsulating of the invention without undue experimentation.

Hence it is clear that the subject matter of the claims presently pending is inventive in view of Chang et al. in combination with Hubbell et al. and/or Pierce Biotechnology, Inc.

The Examiner is thus respectfully requested to reconsider his rejection of the claims under 35 USC § 103.

In view of the above amendment and comments, the application is believed to be in good condition for allowance and a notice to that effect is earnestly solicited.

Respectfully submitted,

NIXON PEABODY, LLP

/Carlos R. Villamar, Reg. # 43,224/
Carlos R. Villamar
Reg. No. 43,224

NIXON PEABODY LLP
CUSTOMER NO.: 22204
401 9th Street, N.W., Suite 900
Washington, DC 20004
Tel: 202-585-8000
Fax: 202-585-8080